Stereochemical control—nitrones from oximes by 1,3-azaprotio cyclotransfer or 1,2-prototropy

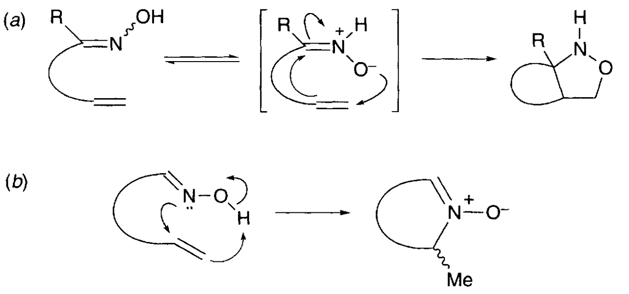
Colm O'Mahony and Frances Heaney*

Department of Chemistry, University College, Galway, Ireland

Oximes 1a,b and 10 are configurationally stable at elevated temperatures, the (*E*)-oximes react exclusively *via* a concerted 1,3-azaprotio cyclotransfer reaction to give 6- and 7-membered cyclic dipoles, respectively, whilst their *Z*-isomers react *via* a 1,2-prototropy–cycloaddition sequence furnishing fused isoxazolidines.

The 1,3-dipolar cycloaddition reaction of nitrones is an important synthetic operation.[1] The most general preparations of nitrones involve the condensation of *N*-substituted hydroxylamines with carbonyl compounds[2] and oxidation of secondary amines.[3] The use of oximes as nitrone precursors has been extensively developed. Oximes react inter- and intra-molecularily with various electrophilic species (*e.g.* alkyl halides, epoxides and electron deficient olefins) to afford *N*-substituted dipoles.[4,5,6] Additionally the prototropic route[7] and the intramolecular 1,3-azaprotio cyclotransfer reaction[5d,e,7c,8] allow nitrone generation from oximes (Scheme 1). One mechanism [Scheme 1(*a*)] produces a small equilibrium concentration of an NH nitrone and is detected only where dipole formation is followed by intramolecular cycloaddition; the other [Scheme 1(*b*)], observed with 'non-activated' γ- and δ-alkenyl oximes, furnishes cyclic nitrones.

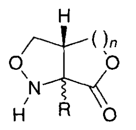
The δ-alkenyl oxime **1a** reacts with electronegative olefins giving the isoxazolidines **2**.[5b] The family of oximes **1** incorporate some of the structural features known to facilitate dipole formation by 1,2-prototropy or cyclization processes namely an sp^2 centre α to the oxime moiety and an allylic electronegative centre in the unactivated alkene.[7] Here we report that in the absence of any external reactant the oximes **1** undergo either a thermally induced 1,2-prototropy-dipolar cycloaddition sequence giving the adducts **3** or a cyclization reaction leading to the dipoles **4**. It was also noted that the stereochemistry of the oxime C–N double bond, a factor which dictates the products of the Beckmann rearrangement, alkylation and nitrosation reactions,[9] influenced the nature of dipole formation for the α-oximino acid esters **1** and the aryl ketoximes **10**.



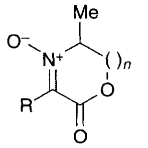
Scheme 1 Dipole formation from oximes: (*a*) tandem 1,2-prototropy–cycloaddition sequence; (*b*) intramolecular 1,3-azoprotio cyclotransfer reaction

The oximes **1** were prepared from their parent α-keto acids, **1a** was obtained as a single diastereoisomer whilst **1b,c** were present as both *E*- and *Z*-isomers. A solution of **1a** was heated in boiling mesitylene for 28 h to furnish the cyclic dipole **4a** (85%) and mixed isomers of the dimeric compound **5a** (*ca.* 5%).† Since oxime *syn*/*anti* interconversion is generally a rapid process, **1b** was reacted as a 2 : 3 mixture of *Z*- and *E*-isomers. After heating in boiling xylene for 30 h the cyclic dipole (**4b**, 54%) was the major reaction product with the bicyclic adduct **3a** (28%), unreacted oxime (10%) and the dimeric species **5b** (8%) also present. Analysis of the crude reaction mixture indicated that the ratio of **4b** to **3a** concurs with the initial ratio of oxime isomers suggesting this oxime is configurationally stable under the reaction conditions. To test this hypothesis the isomers of **1b** were separated by flash chromatography (SiO$_2$, diethyl ether : petroleum spirit, 1 : 4) and characterised, stereochemical assignment was made following inspection of their UV absorption spectra.‡[10] The (*E*)-oxime **6a** reacted exclusively *via* a 6-*exo-trig* cyclization affording (**4b**, 85%) and the *Z*-isomer **7a** reacted more slowly yielding compound **3a** (65%, based on 70% conversion of starting oxime).

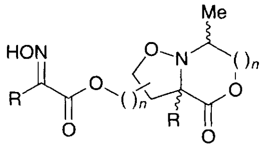
The next homologue, the ε-alkenyl oxime **1c**, was obtained as a 1 : 1 mixture of diastereoisomers which could be separated by flash chromatography (SiO$_2$, diethyl ether : petroleum spirit, 1 : 19). The (*E*)-oxime **6b** reacted more slowly than its analogue **6a**, furnishing the 7-membered cyclic dipole **4c** (35%) follow-



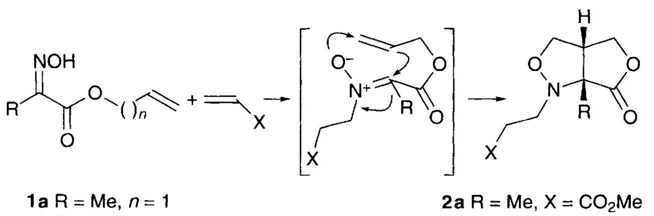
3a R = Ph, *n* = 1
b R = Ph, *n* = 2



4a R = Me, *n* = 1
b R = Ph, *n* = 1
c R = Ph, *n* = 2

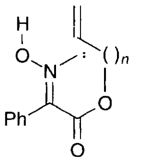


5a R = Me, *n* = 1
b R = Ph, *n* = 1
c R = Ph, *n* = 2

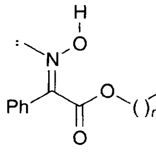


1a R = Me, *n* = 1
b R = Ph, *n* = 1
c R = Ph, *n* = 2

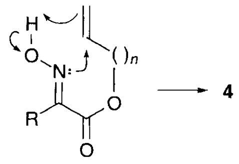
2a R = Me, X = CO$_2$Me
b R = Me, X = SO$_2$Ph



6a *n* = 1
b *n* = 2



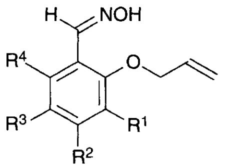
7a *n* = 1
b *n* = 2



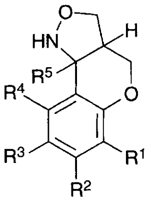
6

ing heating in refluxing xylene for 24 h. Unreacted oxime (65%), surprisingly existing as a 1 : 1.1 mixture of *E*- and *Z*-isomers was also present. The low yield of **4c** may be attributed to the increased entropy of activation required for the formation of a 7-membered ring compared to a corresponding 6-membered ring[11] and to the reversible nature of dipole formation, **4c** reverted to a 1 : 2 mixture of (*E*)- and (*Z*)-oximes upon heating in boiling mesitylene. When the (*Z*)-oxime **7b** was heated in xylene at 140 °C for 60 h there was no **3b** present but instead the crude reaction mixture contained unreacted oxime (75%) as a 2 : 5 mixture of *E*- and *Z*-isomers, the cyclic dipole **4c** (15%) and the dimeric adduct **5c** (7%). The oxime **1c** is thus not configurationally stable upon thermal activation, indeed heating a boiling solution of either the (*E*)- or (*Z*)-oxime in one of mesitylene, xylene or toluene resulted in the formation of cyclic dipole (10–35%) and a 1 : 2 mixture of (*E* : *Z*)-oximes at the equilibrium point.

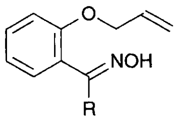
We envisaged that restriction of the conformational mobility of both the oxime and alkenyl moieties may assist in attainment of the transition state required for the 7-*exo*- *trig* cyclization. Substituted aryl aldoximes **8** are converted to the isoxazolidines **9a,b,c** upon thermal activation, the steric buttressing effect of the substituents on the aryl ring promote the reaction which does not otherwise take place.[12] Thus prompted we prepared the oximes **10**, **10a** was obtained solely as the *E*-isomer and upon heating in refluxing xylene (13 h) it quantitatively converted to the dipole **11a**. Oxime **10b** was obtained as a 3 : 1 mixture of *Z*- and *E*-isomers. Following separation (flash chromatography, SiO_2, diethyl ether: petroleum spirit, 3 : 17) and *E*-isomer reacted to give the 6,7-bicyclic nitrone **11b** in 95% yield (xylene, 140 °C, 5 h) whilst the *Z*-isomer reacts more slowly to give the isoxazolidine **9d** (78%, based on 70% oxime conversion).



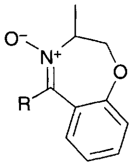
8a $R^1 = R^4 = Me$, $R^2 = R^3 = H$
b R^3, R^4 = CH=CH–CH=CH, $R^1 = R^2 = H$
c $R^2 = R^4 = OMe$, $R^1 = R^3 = H$



9a $R^1 = R^4 = Me$, $R^2 = R^3 = R^5 = H$
b R^3, R^4 = CH=CH–CH=CH, $R^1 = R^2 = R^5 = H$
c $R^2 = R^4 = OMe$, $R^1 = R^3 = R^5 = H$
d $R^1 = R^2 = R^3 = R^4 = H$, $R^5 = Ph$



10 a R = Me
b R = Ph



11 a R = Me
b R = Ph

We thank University College, Galway for support of this work and Cork County V.E.C. and Eolas for a student grant (C. O'M.).

Footnotes

† The addition of 1% *m*/*v* hydroquinone to all the thermal reactions minimises decomposition of the aromatic solvents whilst having no effect on the distribution of product(s).

‡ *E*-Isomers of the α-hydroxyiminoketone chromophore exhibit a bathochromic shift when their spectra recorded in MeOH are compared with those recorded in MeOH/NaOH, *Z*-isomers show no such effect.

References

1 J. J. Tufariello, in *1,3-Dipolar Cycloaddition Chemistry*, ed. A. Padwa, Wiley, New York, 1984, vol. 2, p. 83; P. N. Confalone and E. M. Huie, *Organic Reactions*, Wiley, New York, 1988, vol. 36, p. 1.
2 J. Hammer and A. Macaluso, *Chem. Rev.*, 1964, **64**, 473.
3 S.-I. Murahashi, H. Mitsui, T. Shiota, T. Tsuda and S. Watanabe, *J. Org. Chem.*, 1990, **55**, 1736.
4 R. Grigg, J. Markandu and S. Surendrakumar, *Tetrahedron Lett.*, 1990, **31**, 1191.
5 (*a*) R. Grigg, F. Heaney, S. Surendrakumar and W. J. Warnock, *Tetrahedron*, 1991, **47**, 4477; (*b*) P. Armstrong, R. Grigg, F. Heaney, S. Surendrakumar and W. J. Warnock, *Tetrahedron*, 1991, **47**, 4495; (*c*) R. Grigg, M. J. Dorrity, F. Heaney, J. F. Malone, S. Rajviroongit, V. Sridharan and S. Surendrakumar, *Tetrahedron*, 1991, **47**, 8297; (*d*) R. Grigg, J. Markandu, T. Perrior, S. Surendrakumar and W. J. Warnock, *Tetrahedron*, 1992, **48**, 6929; (*e*) R. Grigg, J. Markandu, S. Surendrakumar, M. Thornton-Pett and W. J. Warnock, *Tetrahedron*, 1992, **48**, 10399.
6 R. Grigg and J. Markandu, *Tetrahedron Lett.*, 1989, **30**, 5489; M. Frederickson, R. Grigg, J. Markandu and J. Redpath, *J. Chem. Soc., Chem. Commun.*, 1994, 2225 and references cited therein; D. Lathbury and T. Gallagher, *Tetrahedron Lett.*, 1985, **26**, 6249.
7 (*a*) R. Grigg, F. Heaney, J. Markandu, S. Surendrakumar, M. Thornton-Pett and W. J. Warnock, *Tetrahedron*, 1991, **47**, 4007; (*b*) A. Hassner, R. Maurya, A. Padwa and W. H. Bullock, *J. Org. Chem.*, 1991, **56**, 2775; (*c*) R. Grigg, J. Markandu, T. Perrior, S. Surendrakumar and W. J. Warnock, *Tetrahedron Lett.*, 1990, **31**, 559.
8 R. Grigg, T. R. Perrior, G. J. Sexton, S. Surendrakumar and T. Suzuki, *J. Chem. Soc., Chem. Commun.*, 1993, 372; R. Bishop, P. R. Brooks and S. C. Hawkins, *Synthesis*, 1988, 997.
9 C. G. McCarty, in *The Chemistry of the Carbon–Nitrogen Double Bond*, ed. S. Patai, Interscience, New York, 1970; M. Anzini, A. Garofalo and S. Vomero, *Heterocycles*, 1989, **29**, 1477; J. F. Hansen, J. A. Easter, D. A. Eckert, K. J. Hunt and D. A. Little, *J. Heterocycl. Chem.*, 1994, **31**, 281.
10 D. H. R. Barton and J. M. Beaton, *J. Am. Chem. Soc.*, 1961, **83**, 4083; P. Baas and H. Cerfontain, *J. Chem. Soc., Perkin Trans. 2*, 1979, 156.
11 J. March, *Advanced Organic Chemistry*, Wiley, New York, 1985, 3rd edn. pp. 185–187.
12 B. S. Oriek, P. G. Sammes and D. J. Weller, *J. Chem. Soc., Chem. Commun.*, 1993, 1412; B. S. Oriek, P. G. Sammes and D. J. Weller, *Tetrahedron*, 1993, **49**, 8179.

Received, 6th September 1995; Com. 5/05907K